1990/871P

THE HIGH COURT

UNITED STATES TOBACCO (IRELAND) LIMITED

AND

UNITED STATES TOBACCO, INC: Plaintiff

IRELAND, THE MINISTER FOR HEALTH

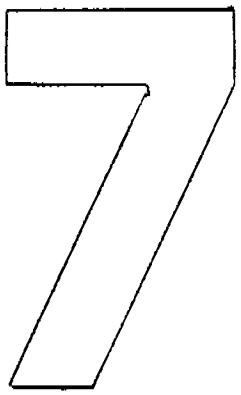
AND

THE ATTORNEY GENERAL: Defendants

ACTION HEARD BEFORE MR. JUSTICE BLAYNEY

IN DUBLIN ON NOVEMBER 27, 1990, AND FOLLOWING DAYS

TRANSCRIPT OF EVIDENCE ON DECEMBER 20, 1990:



I hereby certify the following to be a true and accurate transcript of my shorthand notes of the evidence in the above-named Action.

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TORBJORN MALMFORS, HAVING BEEN SWORN, WAS EXAMINED AS FOLLOWS BY MR. FINLAY:

229 Q. Dr. Malmfors, I think you are Assistant Professor in Toxicology in the Karolinska Institutet in Stockholm?

A. Yes, I am.

230 Q. And you are Swedish by birth and nationality?

A. That is true.

231 Q. And, in relation to your career, there has been a curriculum vitae handed in to Your Lordship. May I briefly refer to some of the aspects of it? Your original qualifications were in medicine. I belief you were a Bachelor of Medicine from the Karolinska Institutet in 1959?

A. That is correct.

232 Q. And that from that institute you also obtained a PhD in 1965.

A. Yes.

233 Q. Followed by a Doctorate in Medicine in 1971.

A. That is correct.

234 Q. And the Karolinska Institutet is in Stockholm. And you have held the position as Teaching Fellow in the Department of Histology from 1958 to 1962 and you have been a research fellow and subsequently an Assistant Professor in the same department?

A. Yes.

235 Q. And you were Associate Professor in the National Institute of Occupational Health in Stockholm and subsequently as Head of Toxicology Laboratories in Astra Pharmaceuticals AB?

A. That is correct.

236 Q. And at present you're a Consultant in Toxicology in the firm of Malmfors Consulting AB?

A. Yes.

237 Q. Of which I believe you are the Principal?

A. I am the Principal of that company, yes.

238 Q. And you have also held the position of Adjunct Professor in the Department of Pharmacology and at present you are Assistant Professor in Toxicology and there you have been an expert in France on

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pharmacology and toxicology to the Minister of Health from 1979 to 1988?

A. Yes.

239 Q. You have published approximately 110 publications on Neurohistology, Neuropharmacology, Toxicology and Risk Assessment.

A. Yes, I have.

240 Q. And I think that added to the curriculum vitae is a list of those publications. You are also a Member of the Scientific Societies including the Swedish Society of Toxicology of which you were President in 1984, the Eurotox, European Societies of Toxicology, the Society of Toxicology, U.S.A., Round Table of Toxicology Consultants, Society for Risk Analysis, American Association for the Advancement of Science?

A. That is correct.

241 Q. And during your career you attended some fifty symposia on Pharmacology and Toxicology?

A. Yes.

242 Q. If I might, at the outset, Dr. Malmfors, in relation to your career, ask you to tell the court what is histology?

A. Histology is also called micranatomy, and it is one of the basis topics in the medical education. That is, you teach medical students how different organs in the body is composed and describe different cells and their components.

243 Q. Can I ask you, Doctor, to tell the court what are nitrosamines?

A. Nitrosamines are a group of chemical compounds which are characterised by a particular combination of oxygen and nitrogen atoms which is found in other nitrosamine atoms.

244 Q. During the evidence which has been given in this, we have heard evidence of tobacco specific nitrosamines - what are they?

A. Tobacco specific nitrosamines are a group of chemical compounds which are characterised by this nitrogen/oxygen parts in the molecule and compounds which are present in different tobacco products.

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245 Q. You say they are present in different tobacco products. Have they been reported to be present in smokeless tobacco products?

A. They have been shown to be present in smokeless tobacco, yes.

246 Q. Are you, generally, familiar with the scientific literature regarding tobacco specific nitrosamines?

A. Yes, I have been following that literature for a couple of years now.

247 Q. Have there been reports in that scientific literature on the relationship between tobacco specific nitrosamines, when tested in isolation, and cancer in laboratory animals?

A. There has been one bit. Excuse me. The tobacco specific nitrosamines have been tested in several animal studies and some of them - not all of them - have been shown to be animal carcinogenic. That means that under experimental conditions they induce tumours of various kinds.

248 Q. As a Toxicologist, how would you describe smokeless tobacco?

A. As a Toxicologist, I look upon smokeless tobacco as what I would like to call a complex mixture of compounds. And why I would emphasise the complex is that it is a real complex issue, and to describe that a little bit more: a complex mixture as smokeless tobacco, there are a lot of different compounds. For instance, in smokeless tobacco, there are probably thousands of different chemical compounds present. And, from a toxicologist point of view, a complex mixture is quite different from a single chemical in respect to a toxicological evaluation.

249 Q. Arising from that, Dr. Malmfors, what is the appropriate method for conducting a toxicological evaluation of a complex mixture such as smokeless tobacco?

A. The only sound way of making a toxicological evaluation of a complex mixture is to test the complete mixture itself.

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250 Q. From the scientific point of view then, is it valid to evaluate such a mixture based on an analysis of a single compound or a group of compounds which may be contained in that complex mixture?

A. No. I think that is scientifically unsound to do such an evaluation, because we know from experience and scientific knowledge that there are a lot of different ways different chemicals can interact in a complex mixture and, as in the case of smokeless tobacco, where there could be thousands of compounds, the number of variations or interactions are numerous and, therefore, it would be absolutely impossible to pass a scientific evaluation just based on an analysis of a single chemical compound in a complex mixture.

251 Q. Could you describe briefly some of the most common possible interactions that might occur between compounds in a complex mixture such as smokeless tobacco?

A. That is a basic knowledge in toxicology which must be taken into consideration. One discusses this. And I, perhaps, can do this, My Lordship, by making a very simple mathematical illustration. Firstly, we have the possibility of two chemical compounds acting together side by side, and they could then be described as one plus one is equal to two. That, we call agonistic. Then, there is the possibility that we have two chemicals working against each other - that is called antagonistic. And, with this simple chemical model we can say that one plus one is less than two. And then the third possibility - which is perhaps incorrectly called interaction - is when two chemicals compounds act on their own, and that I would design by the same chemical model as one plus one equals one plus one. I call this overlapping. And then the fourth type of interaction is when two chemical compounds in the mixture enhance or potentiate each other's affect, then the mathematical formula is one plus one not more than two. This has

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no upper limit and is one of the most serious concerns of interaction between two chemicals in a mixture.

252 Q. Having described agonistic and antagonistic overlapping, would it be possible to give an example of one or more of those interactions?

A. Yes. For instance, agonistic - when two compounds work side by side - I can take the sample of organic solvents. Organic solvents are used on many occasions, and they all quite often mix together. The solvents have one particular effect - that is they affect cell membranes by their pure fat solubility. And it is generally accepted that when we mix solvents together they act agonistically, they act together.

253 Q. And, in relation to antagonism, is there an example?

A. Antagonism in toxicology can also be referred to as antidote therapy. And, the example could be when a child has eaten too many iron tablets - and iron tablets is very hazardous to children - and then one can give drugs which complex bind or bind that iron so that it doesn't exert its toxicological effect. Of course, there are very many other examples but it would be very technical.

254 Q. Would it be a common problem of potentiation or overlapping -

A. If I start with potentiation, there is one case back 20 years ago which might be known, and that is that patients who took medicine for depression - medicines called anti-depressants - of a specific kind, when they ate cheese or bananas or other products which contained monoamines, these anti-depressants caused a potentiation, so the effect of these monoamiens - because they couldn't be broken down in the liver - this increased concentration of monoamines in the body caused increased blood pressure and flush and a lot of symptoms. Regarding overlapping, it's more difficult to give a good example because it is my view that overlapping is a very common thing, that components of a chemical act on their own.

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255 Q. Turning then perhaps to nitrosamines again, doctor. Are you aware of the experimental evidence regarding the possible interaction of nitrosamines purported to be present in smokeless tobacco with other compounds present in smokeless tobacco?

A. Yes, I am familiar with the publication of Hirsch and collaborators in 1986. That study was earlier described by Professor Furst. And, one part of that study specifically addressed the interaction between tobacco specific nitrosamines and the rest of the chemicals in smokeless tobacco or snuff - as it was called in this publication. Perhaps I shall tell, My Lordship, exactly how this experiment was performed because I think this is crucial for the evaluation of the role of nitrosamines in smokeless tobacco. They used rats, they divided them into four groups, about 30 animal per group, and decided to control - the control is very important as Professor Furst described - they treated one group with a water extractive snuff of smokeless tobacco. The treatment was performed by swabbing the solvent in the mouth of the rat five times, five days of the week, for a long time, and they had animals which lived for 131 weeks. The third group, they added to tobacco specific nitrosamines to this snuff extract. They are called NNN and NNK. These two nitrosamines have been shown in animal experiments to be animal carcinogenic. They added about ten times as much as there was in the snuff extract so they could analyse the snuff extract and then they added ten times more of these two tobacco specific nitrosamines. The fourth group of animals were treated with the same concentrates of these two tobacco specific nitrosamines, NNN and NNK. Thus, in the fourth group, no snuff or smokeless tobacco was present. The outcome of this experiment was that in the last group, number four, eight tumours appeared in the mouth of these rats and, compared to the control group, group number one where there was none, there was then a specific statistically significant

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increase. So, one can say that these tobacco specific nitrosamines induced the formation of tumours in those rats. These tumours were characterised as papilloma. Papilloma are a type of tumour which is characterised as a benign tumour. The outcome of group three - which was treated with the same concentrate of tobacco specific nitrosamines dissolved in snuff extract - showed three papilloma. Thus, a lower number than group four. In group two - which was treated with water extracts of snuff only, there was no tumour at all. From those results, the authors as well as I conclude that water extract of snuff does not induce any tumour in the rat while tobacco specific nitrosamines do. Furthermore, when nitrosamines are dissolved in snuff extract there is a lower number of tumours, thus, it is obvious there is an inhibitatory effect of the snuff extract on the formation of tumours by tobacco specific nitrosamines, and you have an example of the antagonism that one plus one is less than two.

256 Q. You have given evidence and given an example from the Hirsch study that the proper way to evaluate a complex mixture is to test the mixture itself rather than its individual compounds or components. Are you aware such tests have been carried out with regard to smokeless tobacco in relation to animals.

A. Yes. Excuse me. I am very familiar with all animal studies which was on that chart. I have reviewed them in detail.

257 Q. Based on your own review of the scientific literature have you formed an opinion as to whether there is any evidence that nitrosamines which were found in smokeless tobacco cause any adverse health effects in users of smokeless tobacco?

A. No. Of course, it is impossible to make this evaluation as it is impossible to make any experiment with human beings. And one can't repeat the study in rats on human beings, and we can't do the individual studies on nitrosamines on man. And, regarding the

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evidence that nitrosamines was present in smokeless tobacco, if they could cause cancer in humans is - according to what I said before - impossible to do.

258 Q. When you say "According to what you said before", is that in regard to the findings of the Hecht study?

A. Yes, and the principle that it is impossible to draw any conclusion on a single component in a complex mixture from experiments or isolations in the complex mixture.

259 Q. In your opinion, Doctor, from a scientific point of view, what would have to be shown or declared in order to conclude that smokeless tobacco is a cause of cancer in humans?

A. Firstly, it is necessary to have evidence or proof that tumour cancer is formed in man, but that is not enough in general. There must be also experimental studies in animals which shows the same thing plus the fact that smokeless tobacco causes cancer in animals.

260 Q. If I just might turn again to the question of nitrosamines, Dr. Malmfors: insofar as the scientific literature deals with the question of nitrosamines in smokeless tobacco products, in your view, is there evidence from the literature that nitrosamines as found in smokeless tobacco products cause adverse health effects to users of those products? Do you understand the question?

A. Could you please rephrase the question?

261 Q. Yes. You have considered scientific literature which deals with these questions of nitrosamines and smokeless tobacco products?

A. Yes.

262 Q. In your opinion, does that literature contain evidence that nitrosamines in smokeless tobacco products cause adverse health effects to users of smokeless tobacco products.

A. No. It is my scientific evaluation that this is not the case.

263 Q. Turning to the broader scientific literature and not really literature dealing with nitrosamines: from your

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own review, as a scientist, of the scientific literature, do you have an opinion as to whether a smokeless tobacco has been shown to be a cause of cancers in users of smokeless tobacco?

A. No. It is my opinion it hasn't been shown.

THE WITNESS WAS CROSS-EXAMINED AS FOLLOWS BY MR. GLEESON:

264 Q. Dr. Malmfors, I understand that you are a Medical Doctor and that you are a specialist in Histopathology - is that correct?

A. No, that is not correct.

265 Q. You are a medical doctor?

A. I am a medical doctor.

266 Q. Histology is the science in which you are an expert?

A. Yes. But, histopathology is slightly different.

267 Q. Does histology involve the examination of cells?

A. It does.

268 Q. Is it the science of the cells?

A. Histology is a science about tissues or the micranatomy, the morphology of the body.

269 Q. In what sense is it incorrect to say that histology is concerned with cells and the changes? Is that incorrect to say?

A. Histopathology is when you deal with a pathological change on the cellular level.

270 Q. But, am I right in thinking that histology is concerned with cells?

A. That is correct.

271 Q. You are a medical doctor and a histologist. You are also a toxicologist, I think, you say?

A. Yes.

272 Q. Who is concerned with the impact of substances on tissues?

A. Yes.

273 Q. Is there any other area in which you wish to claim expertise of the sort of sciences we're talking about here?

A. Histology and toxicology.

274 Q. Are your areas?

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A. Yes.

275 Q. And, as I understand it, what you are talking about here is the chemistry of the compounds found in oral smokeless tobacco and the effect of those compounds - or the absence of the effect of those compounds - on human cells, or animal cells?

A. I'm not talking about the chemistry. I just referred to the characteristics of nitrosamines and I'm dealing with the effect of these nitrosamines on animals and animal experiments.

276 Q. What you're speaking about is the effect which these substances have on animal experiments and animal tissues.

A. That is correct.

277 Q. And that involves an understanding of the compounds in question and the tissues in question.

A. That is correct.

278 Q. Which are the most prevalent carcinogenics in tobacco?

A. I don't know.

279 Q. And, of the tobacco specific nitrosamines - those found only in tobacco, or only so far in tobacco - can you name the two or three that are quantitatively the major known carcinogenics that are present in snuff? Which of the major known carcinogenics which are quantitatively the most significant in terms of their presence in snuff.

A. Those I am talking about, NNN, NNK, NAT.

280 Q. NNN, NNK and NAT.

A. Yes.

MR. JUSTICE BLAYNEY: N -

MR. GLEESON: NNN, NAT and NNK.

A. These are the ones that are most predominantly present. There is also another, NAB. There is also NLA and there is NAB.

281 Q. NAB?

A. Yes.

282 Q. What is NAB?

A. That is nitroanabsine.

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283 Q. How would you rank those compounds, those four or five you have mentioned, in terms of their significance in snuff?

A. It is very difficult to rank them. It depends, with respect, which effect - ?

284 Q. In terms of their carcinogenic potential.

A. Then I have to limit it to animal carcinogenic effects.

285 Q. Very good.

A. NNK is the most potent and NNN is the same. And NAT hasn't been shown to cause cancer in animals. NAB has shown some in one experiment, some tumours, but it is considered a fairly weak animal carcinogenic.

286 Q. Let's look at the two you identify as the most significant, NNK - what is NNK?

A. NNK is a ketone.

287 Q. Can you give me the scientific name?

A. I can't give you the scientific name because my training in chemistry is not so that I easily catch these names.

288 Q. That you don't easily catch the names?

A. Yes, and remember the names.

289 Q. Can you write out the chemical formula for me?

A. I have some idea of it but I don't think that is important for the effect. I know it is a mitrosamine. It has an NO group, which is important.

290 Q. Do you know the chemical formula of NNK, the most significant of the tobacco nitrosamines? Can you write it down?

A. I'm not sure that I can write it down correctly, but I know the principle of those.

291 Q. Can you give me any idea of what the name would be, the name, the chemical structure -

A. It is very difficult to write the structure from the chemical name.

292 Q. Do you know the proper chemical compounds of NNN, the second that you identify?

A. Yes, because that is much easier. It is nitronornicotine (sic).

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293 Q. I think that is nitrosonornicotine?

A. Yes.

294 Q. Do you have any idea what its chemical formula is.

A. I have the same opinion on that. I know.

295 Q. But you couldn't write the compound?

A. I'm saying that I'm not one hundred percent sure that I can write it on the structure.

296 Q. You appreciate that I'm exploring the levels of the chemicals you are speaking about as an expert?

A. That is a knowledge of chemistry where I haven't claimed expertise.

297 Q. But you have been giving authoratitive views to Mr. Finlay as to how chemicals interact. Your evidence is about chemistry, and you have been simplifying it for us. What other known nitrosamines, suggested carcinogenics, have been identified in oral smokeless tobacco?

A. Could you repeat the question please?

298 Q. If we leave aside the nitrosamines, let's just get the factors clear. All chemical compounds are made from a small number of chemical elements - is that right?

A. That's right.

299 Q. How many elements are known now?

A. I think it is 104, but I'm not sure.

300 Q. And every substance known to man is made of some combination of those 104 elements - isn't that right? And the compounds are variable and there are many of them varied and many of them not researched by man?

A. That is right. We estimate the number would be around 5,6, 7 million.

301 Q. The vast majority of which have never been the subject of research.

A. That is correct.

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302. Q. Do you know how many compounds are present in oral smokeless tobacco, approximately?

A. I have seen the figure of 2,500 but I don't think anyone knows exactly the number.

303. Q. Has anyone ever attempted to list the two and a half thousand that they think are present in oral smokeless tobacco.

A. Probably. I haven't seen such a list.

304. Q. You haven't seen such a list.

A. No.

305. Q. How many of the two and a half thousand could you name even by their popular name..

A. I don't know.

306. Q. Would it be more than a hundred.

A. No.

307. Q. Would it be more than fifty or more than twenty.

A. I don't know.

307a Q. Is it more than ten or less than ten.

A. It is probably more than ten.

308. Q. And your interest is, as I understand it, in those components of oral smokeless tobacco which may have unhappy or adverse effects on animal cell tissue, a mutagenic effect, or whatever they may be. Your interest is in those that are known to produce or thought to produce adverse effects on living animal tissues. Now, you have identified some of the nitrosamines, three or four of them. If we turn to the remainder of the list of compounds, the 2,495 that we haven't yet mentioned: which of those are commonly implicated or mentioned as having adverse effects, outside the nitrosamines completely? Does any of those.

A. Yes.

309. Q. Can you name them.

A. Polonium.

310. Q. That is polonium 210.

A. Yes.

311. Q. Tell us about that.

A. Because of its radioactive isotope -

312. Q. Has it been long incriminated as a human carcinogenic.

A. I don't know.

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313.Q. Do you know what sort of levels are found in cigarette tobaccos.

A. No.

314.Q. What other substances come to mind when we're looking at nitromasines being potential cell damagers or cell changers? What other substances in oral smokeless tobacco.

A. There are a lot of organic compounds, and often much in this respect are polyaromatic hydrocarbons.

315.Q. And that is a group of substances you would be familiar with.

A. Yes.

316.Q. They are not esoteric compounds. They are relatively well-known compounds, are they.

A. Yes, they are.

317.Q. Particularly well known to toxicologists.

A. Yes, they are.

318.Q. The polyaromatic hydrocarbons are a particular work of interest among toxicologists worldwide.

A. Yes.

319.Q. Why polyaromatic hydrocarbons.

A. Because they have been used for a lot of experimental work within the field of carcinogens.

320.Q. Is that the only reason.

A. I think that is an important scientific reason. They are also present in different locations and they are also naturally produced compounds which have been described for almost many, many years as a cause of human cancer.

321.Q. If I picked up a toxicology book and looked it up under polyaromatic hydrocarbons, is there any other obvious piece of information I would learn, apart from the fact that they have been implicated as carcinogens and suggested in that connection? Have they been a concern in relation to human health in other instances.

A. Yes. In the field of carcinogenicity, there have been indications that one very ... in the field of carcinogenicity of tar, for instance.

MR. JUSTICE BLANEY: Tar.

A. Tar from coal.

322.Q. MR. GLEESON: And you say that occurs naturally.

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A. They occur naturally.

323.Q. This can also be synthasised.

A. Yes, that is possible.

324.Q. And are synthasised, perhaps -

A. They are synthasised for experimental use, yes.

325.Q. They may be a byproduct of combustion of waste chemicals on occasions.

A. That is true.

326.Q. And that is, of course, of a public health concern in some areas - isn't that right.

A. Yes.

327.Q. People burning solvents, for instance, or waste matter from solvent recovery places - are your familiar with that? Are you, as a toxicologist, familiar with the fact that polyaromatic hydrocarbons are generated in that way.

A. I think we have to make a distinction between polyaromatic hydrocarbons and polypsychic hydrocarbons.

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Q328 MR. GLEESON: What is the process by which the tobacco specific nitrosamines are formed during the process of consuming oral tobacco. Do you know what the chemical process is by which the nitrosamines are formed or how it takes place?

A It's called nitrosylation.

Q329 Nitrosylation?

A Yes.

Q330 From what, what is nitrossed?

A It is the amynes which are nitrossed, A-M-Y-N-E-S.

Q331 MR. JUSTICE BLAYNEY: Sorry?

A Amynes.

Q332 MR. GLEESON: What's the chemical antecedent of the tobacco specific nitrosamines in the tobacco?

A Nicotine.

Q333 Nicotine?

A And it's alkaloids.

Q334 Nicotinic alkaloids?

A Yes.

Q335 What is the process that converts the alkaloids into nitrosamines?

A Nitrosylation.

Q336 How many stages does that go through, the process of nitrosylation?

A I don't know. I don't have that chemical knowledge.

Q337 Have you ever studied that transformation?

A No, I haven't studied that.

Q338 Do you know anything about the life of snuff dippers and the concentrations of the tobacco specific nitrosamines that have been found in the life of snuff dippers?

A I know it's possible to identify these tobacco specific nitrosamines.

Q339 Do you know the concentration?

A I don't remember the concentration.

Q340 Even roughly, within a range?

A No, there are a small concentration but I don't know the numbers.

Q341 Small and big, there is a big range between them. We are now talking about this chemical in the mouths of human beings, the chemistry that you are giving the evidence about on it's affect, are you telling the court that you don't know what the typical figures are for measuring the concentration of nitrosamines?

A It's a range of nanogrammes per millilitre. So it's very small concentrations but I don't remember the figures.

Q342 Could you do it for me in parts per billion, any idea

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at all what the range is in parts per billion?

A I don't remember the numbers.

Q343 Did you ever know, is it a matter of having forgotton or did you at some stage know these figures?

A When I read the paper I see the numbers, yes.

Q344 Is it important in the understanding of the chemistry of the interaction of these substances with living cells to have a good understanding of their own chemistry, the chemistry of substances in question. Is that useful?

A That part of the understanding, yes, it is.

Q345 I am going to read you a statement from a report that enquires as to whether you subscribe to it. "In processing....". (quoted). I think we already agree on that. "The concentrations of the nitrosamines", paraphrasing now, in snuff, exceeds the level of nitrosamines in other consumer products by over one hundred fold. Do you agree with that?

A I can understand, yes, I can understand, that is correct, yes.

Q346 "During snuff dipping of tobacco the nitrosation process, that the process of changing the nicotinic alkaloids into tobacco specific nitrosamines, that that continues with salivation. Is that your understanding?

A That could occur, yes.

Q347 But I want to put the quote from the Surgeon General's report to you at page 66. "During snuff dipping or chewing of tobacco the nitrosylation process", this is the conversion process that we discussed, "continues within the mouth stimulated by oral bacteria". Do you know that to be the case?

A Yes.

Q348 Have you studied the process by which compounds present in oral smokeless tobacco are metabolised in the process of use within the mouth?

A No, I haven't.

Q349 Or the way in which they are changed when they are applied to animal tissue?

A No, I haven't said that.

Q350 Let me just give you one more quote. It's from a summary at page 75 of the Surgeon General's report "Persuasive evidence exists that the carcinogenic nitrosamines that are present in high quantities in snuff and other forms of smokeless tobacco are metabolised", transformed, that means, I take it, Doctor, "by target tissues of experimental animals and by human tissues to intermediates", by

http://legacy.library.ucsf.edu/tid/ovh07a00/pdf http://industrydocuments.ucsf.edu/docs/mjhl0001

intermediates we mean different chemical compounds. Is that right?

A That is right.

Q351 That can modify the genetic material of the cell. Now, do you agree with that?

A Yes.

Q352 So there can be no doubt that the nitrosamines that are present in tobacco can be transformed, metabolised into intermediates, into other chemicals which in turn can modify the genetic material of the cell, can effect the, where way the cell behaves and the way in which it recreates itself?

A That's correct.

Q353 One of the matters that you explained to Mr Finlay was the carcinoginistic affect, if I can put it that way, that chemical compounds can have on each other, that where a chemical compound, a known chemical compound has been studied one may get an idea of it's effects but it's more difficult if you have three different chemicals. They may show in a number of different ways. Is that right?

A That is right.

Q354 And what we are talking about is the number of complications produced by the interaction of different chemicals compounds to produce new and perhaps unknown compounds or certainly unstudied compounds. Is that right?

A That is right.

Q355 And am I correct in thinking that this carcinogy is a very real concern for toxicologists generally, that where you get what is called hot- it's more difficult to describe it's affect because you don't know how the chemicals are going to react with heat or other substances being brought to bear on them?

A That's right, and that's why on the line I point out that the only scientifically valid way of evaluating the complex mixture is to study the complex mixture in full, which has been done in these studies.

Q356 And you think that the isolation of potentially carcinogenic compounds within the two and half thousand compounds is not a particularly useful approach?

A No, I don't think that is meaningful, from a toxicological point of view, to make the evaluation.

Q357 What prospect is there of human science attaining a good understanding of the carcinogy of the two and half thousand compounds that are present in oral [illegible], a true picture of what happens

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when these mixtures are jointly and severally and carcinogised and potentiated and antagonised and so on, when you have this enormous range of possible chemical changes, is there any prospect of human science giving a detailed account of that process in the near future?

A It sounds very difficult, but I don't think that is necessary. I think the point I made here, and I want to repeat that, to make a evaluation of complete complex mixtures is the only way to go.

Q358 Does the expression "a metabolic pathway" mean anything to you?

A Yes.

Q359 Can you just tell us what it means to you?

A It means the series of intermediate metabolites which are formed when a chemical is broken down in the body.

Q360 There is a succession of chemical changes which the various compounds go through as they are transformed in the bodies processes. Is that right?

A That is correct.

Q361 Are you in a position to describe the metabolic pathways for any of the tobacco specific nitrosamines?

A Not in detail.

Q362 Have you ever published on the question of toxicology and tobacco use?

A No.

Q363 Have you ever published on the question of oral tobacco and cancer?

A No.

Q364 Have you ever worked for the tobacco industry in any shape or form as a consultant?

A I have worked as a consultant, yes.

Q365 Could you outline your recent work as fully as possible?

A I worked as a consultant on the question of ETS.

Q366 MR. JUSTICE BLAYNEY: Sorry.

A On ETS, environmental tobacco smoke.

Q367 Environmental tobacco smoke. That's ambient tobacco smoke?

A Yes.

Q368 And to whom are you a consultant?

A To Phillit Morris?

Q369 And is that the full experience?

A And I am also working as a consultant for US Tobacco.

Q370 Can you outline the work you have done for them?

A Giving them scientific evaluations of smokeless

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tobacco.

Q371 Since when?

A For about three years.

Q372 And had you ever worked on smokeless tobacco before that?

A No, I haven't.

Q373 Sorry?

A No, I haven't.

Q374 You haven't. You just started working about three years ago?

A On this particular issue, yes.

Q375 Is that all, Phillit Morris and U-S tobacco.

A Yes.

Q376 No Swedish company?

A No.

Q377 And what has been the nature of your consultancy work over the last three years?

A This work is just part, I also do consultant for other organizations, for other companies.

Q378 I understand that but, sorry, just in relation to US Tobacco,?

A That's the only thing I am doing.

Q379 What sorts of things?

A I have been passing on scientific evaluations on scientific literature.

Q380 Scientific evaluations of scientific literature?

A Yes.

Q381 Have you done any research?

A I haven't done any research, no.

Q382 What sort of brief were you given?

A Parden?

Q383 What was the task that was set you. What were you asked to do?

A I was asked to give my independant scientific view on the scientific issues with regard to smokeless tobacco.

Q384 What are the scientific issues?

A Scientific issues are to evaluate the health effects of smokeless tobacco.

Q385 And what are the health effects of smokeless tobacco that you are evaluating?

A Pardon?

Q386 What health effects of smokeless tobacco are you evaluating the literature on, what were the health effects that you are talking about?

A We are talking about the possible carcinogenic effect.

Q387 Is that the only health effect we are talking about?

http://legacy.library.ucsf.edu/tid/wnp97a00/pdf http://industrydocuments.ucsf.edu/docs/wnpl0001

A That's the main one, yes.

Q388 And do you locate this literature or is it sent to you?

A I get some literature sent. I also look for literature myself.

Q389 And what are you asked to do with the literature when it comes to your hands, either on your own account or it's sent to you. What is the nature of your task at that point in time?

A It's to study, to criticize the literature and pass on these evaluations.

Q390 To what purpose?

A I assume that it is a clients wish to know exactly the scientific backgrounds of their products and it is my understanding that they want to know what type of health effects these products would produce and therefore I think they want an independant expert to evaluate these effects.

Q391 Yes. And typically you would be telling your client about the meaning or worth or value of a scientific paper that had been published?

A Yes.

Q392 And it's possible impact on their business and their product?

A I have no intention to interfere with their business. I just want to tell them what implications those studies have on the health effects.

Q393 And do you write your reports in terms that would be axcessible or comprehensible to nonscientific laymen or are you in correspondance with someone with a doctorate in some science, or at what level do you report?

A I mainly report it orally in such a way that I make sure that it's understood and I mainly pass it on to their counsel, Mr. Finnegan.

Q394 He's a lawyer?

A He's a lawyer.

Q395 Does he have any scientific training, to your knowledge?

A I don't think he has any scientific knowledge but he's very familiar with this literature.

Q396 Do you ever talk to any scientist within the company?

A It has occurred.

Q397 But that's not the usual?

A No, it isn't.

Q398 Do you find it surprising that a distinguished scientist like you should be asked to furnish [illegible] scientific literature neither to the

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general management or to scientific person but to a lawyer. Is that surprising?

A I don't think it's surprising as long as I pass on my evaluation and I do it in such a way that it's understood. That's sufficient for me.

Q399 And what's Mr Finnegans lawyerly interest in this information, do you know, or is that a mystery?

A I don't know.

THE WITNESS THEN WITHDREW

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